CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20-972

STATISTICAL REVIEW

Statistical Review and Evaluation

NDA#: 20,972

APPLICANT: Dupont Pharmaceuticals.

NAME OF DRUG: Sustiva (efavirenz)

INDICATION: Treatment of HIV Infection.

DOCUMENTS REVIEWED: NDA submission and follow-up submissions.

MEDICAL REVIEWER: Harry Haverkos, M.D.

1. Efficacy Results

1.1 Background

This review will focus on 24 week data (accelerated approval) from three phase III trials: Dupont 006, Dupont 020, and ACTG 364. Table 1A contains the treatment arms used in each of the three trials. (Additional trial design information will be provided in the following section.). It can be seen that the three trials investigate the efficacy of efavirenz (EFV) both by attempting to demonstrate similarity or "equivalence" to an approved agent and by demonstrating superiority to placebo. Similarity of effect was to be shown by substituting EFV for another approved drug (indinavir (IDV) in Study 006 and nelfinavir (NFV) in Study ACTG 364) or combinations of drugs (ZDV+3TC in Study 006). Superiority was to be shown by the addition of EFV to other antiretroviral agents (Study 020 and arm 1 versus arm 2 for Study 364). Primary emphasis in this review has been placed upon HIV RNA at 24 weeks (proportion below the lower limit of quantification for the assay used) with CD4 at 24 weeks examined for consistency of treatment effect.

Table 1A: Study Treatment Arms

Arm	Dupont 006	Dupont 020	ACTG 364
1	IDV + ZDV+3TC	IDV + NRTIs[1]	NFV + 2NRTIs[2]
2	IDV + EFV	IDV + NRTIs + EFV	NFV + 2NRTIs + EFV
3	ZDV+3TC + EFV		2NRTIs + EFV

[1]physicians choice of nucleoside reverse transcriptase inhibitors
[2]protocol algorithm, either ddI+d4T or ddI+3TC or 3TC+d4T

This application represents the first time that "equivalence" of effect based upon HIV-RNA (or CD4) has been used to support the approval of a drug for the treatment of HIV. Equivalence (or

more appropriately similarity of effect) in this setting means that the new product has been demonstrated to be sufficiently similar to an accepted control so that it too must be efficacious. It should be kept in mind that the HIV indication does not have a generally accepted minimum difference for demonstrating equivalence. These issues will be discussed in the review.

The Division currently recommends that the establishment of efficacy for an experimental agent based upon similarity of effect will require a study of no less than 48 weeks duration, but that a regulatory action could be taken if the 24 week results are compelling. This means that at 24 weeks the results should be strong enough to predict that the 48-week confidence interval will almost certainly support a conclusion that the treatment is effective. It is required that the trial be allowed to continue until planned completion so that the longer-term results will eventually be provided to the Division. At 48 weeks, ultimate drug approval depends on many factors including: historical cure rate using existing products, the degree of risk associated with treatment failure, and the toxicity of the proposed treatment relative to the control.

The issue of multiple comparisons was discussed with the sponsor prior to submission. Study 006 and ACTG 364 both have two comparisons of an efavirenz-containing arm to a non-efavirenz-containing arm. The sponsor had originally designated a single comparison in each study as primary to avoid a multiple comparisons adjustment. However, the Division indicated prior to submission of the NDA that since both comparisons were of interest, an alpha level of .025 (97.5% confidence interval) would be used to assess equivalence/superiority. In the NDA, the sponsor presented both comparisons as primary but did not use a multiple comparison adjustment. This review reports adjusted confidence intervals.

1.2 Study Designs

This section summarizes the designs of the 3 Phase III studies submitted in the NDA.

Table 1B: Study Designs

	Dupont 006	Dupont 020	ACTG 364
Blinding	Open-label	Double-blind	Double-blind
Weeks of Data	24	24	24
Study Population			
Prior NRTI	3TC naïve	Experienced	Experienced
Prior PI	Naïve	Naïve	Naïve
Prior NNRTI	Naïve	Naïve	Naïve
CD4 entry	>50 cells	>50 cells	No restriction
HIV-RNA entry	> 10,000 copies	> 10,000 copies	>500 copies
Primary Endpoint	RNA <400 copies	RNA <400 copies	RNA <500 copies*

*ACTG uses a lower limit of 500 copies based upon their review of assay performance at ACTG certified laboratories

1.3 Study Demographics

This section summarizes the baseline demographics of the subjects in the 3 studies.

Table 2: Study Demographics

	Dupont 006	Dupont 020	ACTG 364
Number Randomized	450	282	196
Number Receiving Drug	431	282	195
Baseline Characteristics			
Mean HIV-RNA	4.77 log (59,000)	4.38 log (24,000)	3.91 log (8,100)
Mean CD4	345 cells	333 cells	388 cells
Mean Age	36 years	38 years	41 years
Race	60% Caucasian	54% Caucasian	74% Caucasian
Gender	86% male	80% male	88% male
Years HIV-Positive	3.2	6.1	NA

Demographics and baseline characteristics were well balanced across treatment arms in each study.

1.4 Study Results

This section summarizes the efficacy results for the three Phase III studies in the NDA. All subjects randomized were included in the efficacy analyses. The primary endpoint was the percent of patients with HIV-RNA less than the assay limit at 24 weeks. The sponsor presented several methods of handling missing data: non-completer equals failure (NCF), observed data only, and last observation carried forward. The NCF analysis is generally viewed as the preferred analysis, but the results from additional analyses will also be discussed in the review. The comparison of the results from these other analyses will be of greater importance in Study 006 (open-label) where there was a higher rate of non-completion in the control arm.

The results presented in the review differ somewhat from the NDA. First, as discussed in Section 1.1, the sponsor did not include multiple-comparisons confidence intervals for the two studies where such an adjustment was necessary. This section reports the adjusted confidence intervals where appropriate. Second, the sponsor did not use the full denominator when calculating the percent of subjects below 400 or (b)(4)----- Previous reviews have permitted censoring of subjects with missing RNA values only when the subjects were known to be below 400 copies both before and after the missing value. The sponsor did not apply this rule in the initial NDA submission. While the number of subjects excluded in the NDA analyses by the sponsor was small, this review uses the full denominator in the analyses. Unless otherwise noted, p-values for comparisons of the percent of subjects less than the assay limit are calculated using Fisher's Exact Test.

1.4.1 Study 006

Study 006 was an open-label study in 3TC naïve, PI naïve, and NNRTI naïve patients. The majority of patients were also ZDV naïve (390/450, 87%).

1.4.1.1 Patient Disposition

Table 3: Study 006 Patient Disposition

	IDV+ZDV+3TC	EFV+ZDV+3TC	EFV+IDV
Randomized	148	154	148
Completed 24 Weeks	92 (62%)	122 (79%)	113 (76%)
Dropouts	56 (38%)	32 (21%)	35 (24%)
Not Dosed	6	6	7
Adverse Event	26 (17.6%)	10 (6.5%)	7 (4.8%)
Lack of Efficacy	0	0	1
Protocol Violation	9	3	9
Withdrew consent	6	3	3
Lost to Follow-up	9	10	7
Other	0	0	1

There was a very high discontinuation rate in the control arm in this study. If this imbalance in dropouts were mainly do to lack of efficacy then this fact would not be of concern in interpreting the results of the trial, since the primary analysis considers non-completers as failures. However, the imbalance appears to be due to adverse event related dropouts (see Table 3). Since the study was open-label, it is possible that these dropouts were influenced by the knowledge of the treatment assignment. In fact, several factors lead to the conclusion that this may have occurred for some patients. First, if the IDV component of the regimen was primarily responsible for the AE-related dropouts, then this should have been seen in the EFV+IDV arm. If the ZDV+3TC component of the regimen was primarily responsible for the AE-related dropouts, then this should have been seen in the EFV+ZDV+3TC arm. Most likely both IDV and ZDV+3TC contributed to the dropouts, but still the AE-related dropout rate was higher than the total of the rates in the other two arms (17.6% vs. 11.3%). Thus an imbalance remains even assuming that efavirenz caused no AE-related dropouts. Second, a review of the patients who dropped out suggested that the adverse events that lead to discontinuation in the control arm may have been milder than those in the efavirenz-containing arms (see Medical Review). Given the open-label nature of the study, the differential in discontinuations means that overall conclusions drawn from this study must be considered less robust than if the study were double-blind or if discontinuations had been a result of a rigorously defined algorithm.

Since dropouts are considered to be virologic failures in the primary analysis, these dropouts impacted the analysis substantially. The next section discusses the effect of the dropouts on the results and interpretation of the study.

1.4.1.2 HIV-RNA

Table 4: Study 006 HIV-RNA Results

	IDV+ZDV+3TC	EFV+ZDV+3TC		EFV+IDV	
Assay Lower Limit	% success	% success	97.5% CI*	% success	97.5% CI*
400 copies	82/148 (55.4%)	109/154 (70.8%)	3%, 28%	93/148 (62.8%)	-5%, 20%
(b)(4)----	----------	----------	----------	----------	----------

*confidence interval on the difference relative to IDV+ZDV+3TC, positive numbers indicate comparative advantage of EFV-containing regimens

For the primary analysis of the percent less than 400 copies, given the observed numeric superiority and the lower confidence bounds, it can be concluded that the efficacy of efavirenz has

been established through the similarity of both efavirenz-containing regimens to the control arm. In the NDA, the sponsor made the additional claim of superiority of EFV+ZDV+3TC over the control arm. This section will examine this claim in light of the differential in dropouts.

If subjects with missing data due to adverse events or the withdrawal of consent are excluded, the success rates go up in each arm (see Table 5). The EFV+ZDV+3TC arm is still numerically superior with a reasonably tight confidence interval. Clearly, though, the claim of superiority of EFV+ZDV+3TC can no longer be supported. In addition, the EFV+IDV arm has a lower success rate than the control arm. In this analysis at 24 weeks, the results for EFV+IDV no longer conclusively demonstrate similarity of effect relative to the control. Overall, it appears that the analysis of this subset of subjects is less supportive of the claims that EFV is superior to IDV and similar in efficacy to ZDV+3TC. Given the likelihood of bias introduced by the open-label nature of the study, this alternative analysis may be more representative of the true relative efficacy of the arms.

Table 5: Study 006 HIV-RNA Results (Adverse Event Dropouts Excluded)

	IDV+ZDV+3TC	EFV+ZDV+3TC		EFV+IDV	
Assay Lower Limit	% success	% success	97.5% CI*	% success	97.5% CI*
400 copies	82/116 (70.7%)	109/141 (77.3%)	-6%, 19%	93/138 (67.4%)	-16%, 10%

*confidence interval on the difference relative to IDV+ZDV+3TC, positive numbers indicate comparative advantage of EFV-containing regimens

Therefore, while the results seen in this study demonstrate the efficacy of efavirenz, they do not demonstrate superiority of either of the two efavirenz-containing arms over the control arm. Further, they suggest that the present study may be too small to evaluate the relative efficacy of EFV+IDV and IDV+ZDV+3TC.

In the assessment of the efficacy of EFV in the above comparisons it is important to consider the historical results for the proportion below the limit of the assay for ZDV+3TC and IDV monotherapy in the absence of EFV. This will aid in the interpretation of the confidence intervals. In Merck Study 028 (see Statistical Review for NDA 20-685) the proportion of subjects below the limit of the assay was approximately 30% based upon 332 subjects randomized to indinavir monotherapy. The rough 95% confidence interval (ignoring stratification) is 30% +/- 5. A second study in naïve subjects, study 033 reviewed for the accelerated approval of indinavir, had a proportion below the limit of the assay of approximately 45% based upon 81 subjects. The confidence interval for this result is 45% +/- 11%. Both of these study results suggest, even with the difficulties associated with making comparisons across studies, that the observed effect for EFV+IDV is comfortably above an expected treatment effect for indinavir monotherapy.

Historical results for the use of ZDV+3TC in a similar population (essentially antiretroviral naïve) can be obtained from Agouron Study 511 (see Statistical Review for NDA 20-779), which was used to support the approval of nelfinavir for the treatment of HIV. In that study, approximately 30% of the subjects attained the limit of the assay (b)(4)----------, (b)(4)---------- (b)(4)---------- This suggests that the lower bound of the confidence interval on the difference between IDV+ZDV+3TC and IDV+EFV (-16% in the alternative analysis) supports the efficacy of EFV.

1.4.1.3 CD4

Table 6: Study 006 CD4 Results

	IDV+ZDV+3TC	EFV+ZDV+3TC		EFV+IDV	
	Mean Change	Mean Change	97.5% CI*	Mean Change	97.5% CI*
24 Week Data	+137	+141	-34, +42	+152	-27, +56
Subjects with Data	91/148 (61%)	113/154 (73%)		105/148 (71%)	

*confidence interval on the difference relative to IDV+ZDV+3TC, positive numbers indicate comparative advantage of EFV-containing regimen

The treatment arms were associated with roughly comparable CD4 increases. As is evident from the wide confidence intervals, this study is not large enough to precisely estimate the relative CD4 effects. In addition, the large number of subjects without 24 week data produces further uncertainty in the estimates.

1.4.2 Study 020

Study 020 was a double blind study in patients with NRTI experience. Physicians were allowed discretion in the choice and number (up to 2) of NRTIs to use concomitantly.

1.4.2.1 Patient Disposition

Table 7: Study 020 Patient Disposition

	EFV+IDV+NRTIs	IDV+NRTIs
Randomized	136	146
Completed 24 Weeks	96 (71%)	112 (77%)
Dropouts	40 (29%)	34 (23%)
Not Dosed	0	0
Adverse Event	16 (12%)	9 (6%)
Lack of Efficacy	0	1
Protocol Violation	5	6
Withdrew consent	10	11
Lost to Follow-up	7	7
Other	2	0

There was a slightly higher rate of discontinuation due to adverse events in the efavirenz arm. The discontinuation rate due to adverse events in the control arm (6%) can be contrasted to study 006 where it was noted that the IDV+ZDV+3TC arm had a high discontinuation rate (18%). Since Study 020 was double-blinded, this small AE-related dropout rate supports the caveats to the interpretation of Study 006 that were raised in Section 1.4.1.

1.4.2.2 HIV-RNA

Table 8: Study 020 HIV-RNA Results

Assay Lower Limit	IDV+NRTIs % success	EFV+IDV+NRTIs % success	p-value
400 copies	73/146 (50%)	79/136 (58%)	.19
(b)(4)----	----------	----------	---

The difference in the proportion below 400 copies at 24 weeks, while numerically favoring EFV, did not achieve statistical significance. (b)(4)----------

(b)(4)----------

1.4.3.2 will discuss the results of ACTG 364, which contained a very similar comparison: the addition of EFV on a background of a protease inhibitor and 2NRTIs in treatment experienced subjects. Overall, when considered in the context of the set of trials in the NDA, this study does provide supportive evidence of efficacy.

1.4.2.3 CD4

Table 9: Study 020 CD4 Results

	IDV+NRTIs	EFV+IDV+NRTIs	p-value	95% CI
24 Week Data	+103	+119	.39	-16, +49
Subjects with Data	105/146 (72%)	86/136 (63%)		

The treatment arms were associated with roughly comparable CD4 increases. As is evident from the wide confidence intervals, this study is not large enough to precisely estimate the relative CD4 effects. In addition, the large number of subjects without 24 week data produces further uncertainty in the estimates.

1.4.3 Study ACTG 364

Study ACTG 364 was a double-blind study in patients with a long duration of prior NRTI use but were PI and NNRTI naïve.

1.4.3.1 Patient Disposition

Table 10: Study 364 Patient Disposition

	NFV+2NRTIs	EFV+2NRTIs	EFV+NFV+2NRTIs
Randomized	66	65	65
Completed 24 Weeks	63	63	59
Dropouts	3	2	6
Not Dosed	0	0	1
Adverse Event	0	1	2
Lack of Efficacy	3	1	0
Protocol Violation	0	0	1
Withdrew consent	0	0	2
Lost to Follow-up	0	0	0
Other	0	0	0

This study is notable for having a very low discontinuation rate. The likely explanation is that patients were only eligible for this study if they had fully completed two other prior ACTG studies (see Medical Review for more details). These patients, therefore, were selected for their proven ability to be compliant with study medications and follow-up. Thus, this patient population may not be representative of those who might receive the drug in a non clinical trial setting.

1.4.3.2 HIV-RNA

Table 11: Study 364 Week 24 HIV-RNA Results

	NFV+2NRTIs	EFV+2NRTIs		EFV+NFV+2NRTIs	
Assay Lower Limit	% success	% success	97.5% CI*	% success	p-value*
500 copies	29/66 (44%)	38/65 (58.5%)	-5%, 34%	46/64 (72%)	.002

*difference relative to NFV+2NRTIs

On the basis of these results, it can be concluded that the 4 drug arm is superior to the NFV control arm. This result also means that the marginal finding in Study 020 is of less concern, since the very similar comparison here (efavirenz+protease+2NRTI vs. protease+2NRTI) is so solid. The comparison based upon the substitution of EFV for nelfinavir in this study supports the efficacy of EFV based upon the numeric superiority and the lower bound of –5% for the difference. It seems reasonable that for the present population there would be a relatively low proportion of patients with HIV RNA below the LOQ at 24 weeks on a regimen of dual-nucleoside therapy only. This being the case, the observed results provide further support for concluding than EFV is efficacious.

1.4.3.3 CD4

Table 12: Study 364 Week 24 CD4 Results

	NFV+2NRTIs	EFV+2NRTIs		EFV+NFV+2NRTIs	
	Mean Change	Mean Change	97.5% CI*	Mean Change	p-value*
24 Week Data	+69	+80	-29, +53	+47	.47

*difference relative to NFV+2NRTIs

Nearly all (97%) of the subjects had week 24 CD4 values. The treatment arms were associated with roughly comparable CD4 increases. As is evident from the wide confidence intervals, this study is not large enough to precisely estimate the relative CD4 effects. There were no significant differences between the groups, although the 4 drug regimen had the smallest change from baseline (difference in mean change of -22 cells relative to control; CI: –81 to +37). It is unlikely that this represents an adverse effect of efavirenz on CD4 since the 3 drug regimen with efavirenz had the largest CD4 response. Further, this difference was not significant and was not seen in the other studies with similar regimens and comparisons (including the controlled phase II studies).

(b) (4)----------

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3. Review Conclusions

The NDA provides clear and compelling results that demonstrate efavirenz is effective for reducing HIV-RNA levels. The NDA included 3 phase III clinical trials, each using the current standard of care (a protease plus two nucleosides) as the control regimen. In these trials, efavirenz was studied in 2, 3, and 4 drug regimens, both with and without a protease, and in treatment experienced and treatment naïve subjects. However, there are statistical issues that need to be kept in mind while interpreting the results of these studies. Study 006 suffered from a differential dropout rate that may have been a result of the open-label nature of the study. This suggests that though there has been a demonstration of efficacy from Study 006, the relative efficacy of efavirenz and indinavir can not be assessed from this study. Study 020 did not yield a significant difference between efavirenz and placebo in the primary analysis. And Study ACTG 364 used a highly select group of patients. While each of the three studies have weaknesses individually, these weaknesses are not overlapping, so that in the end the package as a whole provides strong evidence that efavirenz is effective for the treatment of HIV.

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This review contains 9 pages